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Sharon Rawls
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Signature

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

Lynn E. Spitler et al.

Serial No.: 08/105,444

Filing Date: 11 August 1993

Title: PROSTATIC CANCER VACCINE

Group Art Unit: 1806
Examiner: P. Gambel

SUPPLEMENT TO SUBMISSION UNDER
37 C.F.R. § 1.116 Filed 7 July 1995

Box AF

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

On 7 July 1995, a response was filed herein which, on page 5, referred to a reference enclosed describing an antigen newly discovered as associated with prostate tissue- i.e. prostate specific mucin. In reviewing the file, applicants have found that specific citation to the reference was omitted and that the reference itself was not enclosed. The present submission is to correct this omission and to elucidate further the rationale for the claimed vaccine.

The missing references whose enclosure was intended were abstracts of the following articles:

Wright, G.L. Jr. et al
Int. J. Cancer (1991) 47:717-725

Beckett, M.L. et al Cancer Res. Search
(1991) 51:1326-1333.

These abstracts describe an antigen associated with prostate carcinomas other than PSA, PSMA, and PAP.

In the first abstract, a series of sialic acid containing glycoprotein representing a complex was recognized by a monoclonal antibody designated TURP-27. The authors conclude that this prostate carcinoma-associated sialyl glycoprotein complex (PAC) recognized by MAb TURP-27 is likely to represent a novel tumor antigen expressed by prostate tumors.

Similarly, the second article describes reactivity of various tissues to a monoclonal antibody designated PD41. The abstract concludes "it appears that this monoclonal antibody may recognize a prostate carcinoma-associated mucin-like antigen, which is preferentially expressed on prostate carcinomas, and therefore, may be a useful marker to distinguish benign prostate hyperplasia from prostate carcinoma."

These abstracts are adduced simply for the proposition that there are undoubtedly additional antigens characteristic of prostate tissue in general, or prostate carcinoma in particular, that would be useful in the method of the invention. The invention is not directed to these antigens *per se*, but rather the appreciation that they are suitable candidates for vaccines directed specifically against prostate cancer.

Only the applicants have successfully recognized the generality of this concept. For example, prostate specific antigen (PSA) is not a membrane protein. Therefore, one might assume that it would be ineffective as a vaccine as it is not associated *per se* with the membrane of the target cell. Indeed, as PSA is secreted into the plasma, antibodies raised against PSA would be expected to

act on this circulating molecule, rather than directly on the tumor cells. On the other hand, it has been appreciated by the present applicants that proteins produced in any particular cell have peptides represented on the cell surface in the context of MHC1 and MHC2 histocompatibility antigens. It is these complexes that can be recognized by the immune system, and specifically by cytotoxic T-lymphocytes. Thus, even though PSA *per se* is not represented on the membrane, its peptides are displayed on the cells bearing these peptides would be subject to attack by cytotoxic T-lymphocytes. Applicants' appreciation of this mechanism and its relationship to designing vaccines is not suggested by the art and permits the generalization set forth in the present claims.

Applicants respectfully request that this Supplementary Amendment be considered along with that previously submitted. In view of the time frame subsequent to final rejection, a Notice of Appeal is also submitted herewith. (Both this Response and the Notice of Appeal are being mailed first class mail; a copy of this supplementary response is also being submitted by fax.)

Respectfully submitted,

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Unique Identifier

91145874

Authors

Beckett ML. Lipford GB. Haley CL. Schilhamer PF. Wright CL Jr.

Title

Monoclonal antibody PD41 recognizes an antigen restricted to prostatic adenocarcinomas.

Institution

Department of Microbiology and Immunology, Eastern Virginia Medical School, Norfolk 23501.

Journal

Cancer Research. [JC:cnf] 51(4):1326-33, 1991 Feb 15.

Abstract

A monoclonal antibody (MAB) designated PD41 (IgG1k) was generated by hyperimmunizing BALB/c mice with a membrane preparation prepared from a moderately to poorly differentiated prostate carcinoma surgical specimen. The immunohistochemical reactivity of MAB PD41 was shown to be highly restricted to the ductal epithelia and secretions of prostate adenocarcinoma tissues. Sixty-five % of the prostate tumor specimens were stained with MAB PD41, whereas no staining of the fetal or benign prostate specimens was observed. PD41 reacted minimally with normal prostate tissues, with less than 1% of the epithelial cells staining. This MAB did not react with nonprostate carcinomas or to a variety of normal human tissues. Using both radioimmunoassay and immunofluorescent procedures, several cultured human tumor cell lines, human blood cells, and purified antigens to prostate-specific antigen and prostatic acid phosphatase also were found not to express the PD41 antigen. MAB PD41 also was shown to bind to the target antigen present in seminal plasma obtained from prostate carcinoma patients but not to seminal plasma from normal donors. Immunoblots of gel-separated components of prostate carcinoma tissue extracts indicate that the molecular weight of the proteins carrying the PD41 antigenic determinant can differ among individual tumors, ranging from Mr 90,000 to greater than 400,000. However, in seminal plasma from prostate cancer patients, the predominant component recognized by PD41 is the diffuse Mr greater than 400,000 band. It appears that this monoclonal antibody may recognize a prostate carcinoma-associated mucin-like antigen, which is preferentially expressed on prostate carcinomas, and therefore, may be a useful marker to distinguish benign prostate hyperplasia from prostate carcinoma.

Uniqu Identifier
91169686

Authors

Wright GL Jr. Beckett ML. Lipford GB. Haley CL. Schellhammer PF.

Title

A novel prostate carcinoma-associated glycoprotein complex (PAC) recognized by monoclonal antibody TURP-27.

Institution

Department of Microbiology and Immunology, Eastern Virginia Medical School, Norfolk 23501.

Journal

International Journal of Cancer. [JC:ggu] 47(5):717-25, 1991 Mar 12.

Abstract

A prostate carcinoma-associated antigen recognized by MAb TURP-27 was characterized immunohistochemically and biochemically. TURP-27 antigen was found localized in the cell membrane and cytoplasm of the ductal epithelial cells of normal (10%), benign (75-100%) and malignant (20-100%) prostate cells. Fetal prostate tissues were also found to express the TURP-27 antigen, suggesting expression early in development. This antigen was not expressed by non-prostate tumors examined, but significant cross-reactivity was observed in myelinated nerves while minor cross-reactivity was seen in certain lymphocyte subsets, cells in the adrenal medulla and chief cells of stomach. Immunoblotting and biochemical data demonstrated that the TURP-27 antigen is a sialic-acid-containing glycoprotein complex with major molecular species in prostate tissues of 310-250, 180, 140, 115, 95-90, 69, and 40- to 35-kDa. Immunoblotting patterns similar to those observed for prostate tissues were also seen in CNS extracts with the exception of the 69 and 40- to 35-kDa proteins. This prostate carcinoma-associated sialoglycoprotein complex (PAC) recognized by MAb TURP-27 is likely to represent a novel tumor antigen expressed by prostate tumors.